Ophthalmic Antibiotic–Steroid Combinations Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS[1,2,3,4,5]

All of the listed drugs are indicated for corticosteroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where bacterial infection or a risk of bacterial infection exists.

Drug	Strength	Manufacturer
dexamethasone / neomycin sulfate/ polymyxin B sulfate (Maxitrol®)	0.1%; EQ. 3.5 mg base/ml; 10,000 units/ml	generic (suspension, ointment)
dexamethasone / tobramycin (Tobradex®)	0.1%; 0.3%	generic (suspension, ointment)
dexamethasone / tobramycin (Tobradex®ST)	0.05%; 0.3%	Alcon (suspension)
hydrocortisone / neomycin sulfate / polymyxin B sulfate	1%; EQ 3.5 mg base/ml; 10,000 Units/ml	generic (suspension)
hydrocortisone / bacitracin zinc / neomycin sulfate / polymyxin B sulfates	1%; 400 Units/gm; EQ 3.5mg Base/gm; 10,000 Units/gm	generic (ointment)
loteprednol / tobramycin (Zylet™)	0.5%; 0.3%	Bausch & Lomb (suspension)
prednisolone acetate / gentamicin sulfate (Pred-G®)	EQ 0.3% Base; 1%	Allergan (suspension)
prednisolone acetate / gentamicin sulfate (Pred-G® S.O.P)	EQ 0.3% Base; 0.6%	Allergan (ointment)
prednisolone acetate / sulfacetamide sodium (Blephamide®, Blephamide® S.O.P.)	0.2%; 10%	generic (suspension, ointment)
prednisolone sodium phosphate / sulfacetamide sodium	EQ. 0.23% phosphate; 10%	generic (solution)

OVERVIEW

Infections of the eye can rapidly damage important functional structures and lead to permanent vision loss or blindness. A corticosteroid will reduce inflammation and, when combined with an antibiotic, the antibiotic treats or prevents an infection, which may be associated with the inflammation.

PHARMACOLOGY

Corticosteroids provide local anti-inflammatory activity. Dexamethasone, hydrocortisone, loteprednol, and prednisolone provide local anti-inflammatory activity. Loteprednol is an analog of prednisolone and induces slightly less elevation of intraocular pressure (IOP) compared to prednisolone.[6]

Antibiotics provide local antibacterial activity in the respective spectrums. Selection of the antibiotic should depend on the known or suspected organisms involved in the potential or present infection.

Aminoglycosides, which include gentamicin, neomycin, and tobramycin, inhibit protein synthesis by binding to the 30S ribosomal subunit.

Polymyxin B is bactericidal for a variety of gram-negative organisms. It increases the permeability of the bacterial cell membrane by interacting with the phospholipid components of the membrane.

Bacitracin, which is bactericidal, inhibits bacterial growth through prevention of the addition of cell wall subunits to the peptidoglycan chain.

Sulfacetamide is a synthetic sulfonamide that inhibits bacterial dihydrofolate synthetase, a bacterial enzyme responsible for the conversion of *p*-aminobenzoic acid (PABA) into folic acid. Production of folic acid is an essential component of bacterial development.

PHARMACOKINETICS

Ophthalmic ointments have the longest contact time between the drug and the ocular tissues; however, ointments can impede delivery of other ophthalmic drugs by serving as a barrier. Ointments are useful in children so as to decrease the loss of drugs by tears. Ophthalmic suspensions mix with tears less rapidly and remain in the cul-de-sac longer than solutions. Systemic absorption of these products is minimal.

CONTRAINDICATIONS/WARNINGS[7,8,9,10,11,12,13,14,15]

These combination agents are contraindicated in most viral diseases of the cornea and conjunctiva, in mycobacterial infection of the eye, and fungal diseases of ocular structures.

Prolonged use of corticosteroids may result in glaucoma, as well as increase the hazard of secondary ocular infections. Corticosteroids should be used with caution in the presence of glaucoma. If corticosteroid-containing ophthalmic preparations are used for ten days or longer, IOP should be monitored even though it may be difficult in children and uncooperative patients.

DRUG INTERACTIONS

Based on the minimal extent of absorption with these agents, interactions with systemically administered drugs are unlikely to occur.

ADVERSE EFFECTS[16,17,18,19,20,21,22,23,24]

Most effects are related to local irritation on instillation. Occasionally, allergic sensitization (e.g., itching, swelling, and conjunctival erythema) may occur. Serious hypersensitivity reactions (e.g., anaphylaxis) are rare.

Corticosteroids have been associated with elevated IOP with possible development of glaucoma, infrequent optic nerve damage, posterior subcapsular cataract formation, and delayed wound healing. Studies in healthy volunteers showed loteprednol/tobramycin (Zylet) to cause less increase in IOP and better tolerability compared to dexamethasone/tobramycin (Tobradex).[25,26] Elevations in intraocular pressure should not be clinically significant with short-term use.

Secondary fungal and viral infections have been reported.

Adverse effects data are compiled from package inserts and cannot be considered comparative or all inclusive.

SPECIAL POPULATIONS[27,28,29,30,31,32,33,34,35,36]

Pediatrics

Safety and effectiveness of these agents in pediatrics have not been established, with the exception of tobramycin/dexamethasone (Tobradex, Tobradex ST) and neomycin/polymyxin B/dexamethasone (Maxitrol), which has been established in patients two years and older. Data are available for patients older than two months for prednisolone/sulfacetamide (Blephamide).

In clinical trials, loteprednol/tobramycin (Zylet) did not show efficacy for lid inflammation or blepharoconjunctivitis in pediatric patients aged zero to six years.

Pregnancy

All products in this class are Pregnancy Category C.

DOSAGES[37,38,39,40,41]

Apply to affected eye(s).

Drug	Ointment Dosage	Dropper Dosage	Availability
0.1% dexamethasone / 0.35% neomycin base / 10,000 units polymyxin B sulfate (Maxitrol)	Apply every 3 to 4 hours	1 to 2 drops every 3 to 4 hours	5 mL suspension, 3.5 g ointment
0.1% dexamethasone / 0.3% tobramycin (Tobradex)	½ inch up to 3 or 4 times daily	1 to 2 drops every 4 to 6 hours. During the first 24 to 48 hours, the dosage may be increased to 1 to 2 drops every 2 hours.	2.5, 5, and 10 mL suspension, 3.5 g ointment
0.05% dexamethasone / 0.3% tobramycin (Tobradex ST)	--	1 drop every 4 to 6 hours. During the initial 24 to 48 hours, dosage may be increased to 1 drop every 2 hours.	5 mL suspension
1% hydrocortisone / 0.35% neomycin sulfate / 10,000 units polymyxin B suspension	--	1 to 2 drops every 3 to 4 hours	7.5 mL suspension
1% hydrocortisone / 0.35% neomycin base / 400 units bacitracin zinc / 10,000 units polymyxin B ointment	Apply every 3 to 4 hours	--	3.5 g ointment
0.5% loteprednol / 0.3% tobramycin suspension (Zylet)	--	1 to 2 drops every 4 to 6 hours; during the first 24 to 48 hours, may increase to 1 to 2 drops every 2 hours	5 and 10 mL suspension
1% prednisolone / 0.3% gentamicin base suspension (Pred-G) 0.6% prednisolone / 0.3% gentamicin base ointment (Pred-G S.O.P.)	½ inch 1 to 3 times daily	1 drop 2 to 4 times daily; May increase to 1 drop every hour during first 24 to 48 hours	5 mL suspension, 3.5 g ointment
0.23% prednisolone / 10% sulfacetamide solution 0.2% prednisolone / 10% sulfacetamide suspension (Blephamide) 0.2% prednisolone / 10% sulfacetamide ointment (Blephamide S.O.P.)	½ inch up to 3 or 4 times daily	1 to 3 drops every 1 to 4 hours	5 and 10 mL solution/ suspension, 3.5 g ointment

CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Very little good quality comparative data have been published for the products in this class.

tobramycin/dexamethasone (Tobradex) and tobramycin/loteprednol (Zylet)

In a double-blind, randomized trial, tobramycin/dexamethasone and tobramycin/loteprednol were compared for effectiveness in controlling inflammation in 40 patients with blepharo-keratoconjunctivitis.[42] Patients received tobramycin 0.3%/dexamethasone 0.1% or tobramycin 0.3%/loteprednol 0.5% twice daily in the test eye. Baseline evaluation recorded the severity of blepharitis, conjunctivitis, ocular discharge, and corneal punctuate epithelial keratopathy on a scale of three (extensive) to zero (minimum) for each component. Patients with a total score of greater than six were included in the trial. After three to five days, the ocular surface was re-evaluated for treatment response. No significant differences were noted between the groups at baseline. Mean post-treatment scores were as follows: total ocular surface scores, 1.8 and 3.4 (p=0.002); blepharitis scores, 0.9 and 1.35 (p=0.017); discharge scores, 0.2 and 0.6 (p=0.025); and conjunctivitis scores, 0.15 and 0.6 (p=0.013) for tobramycin/dexamethasone and tobramycin/loteprednol, respectively. Corneal punctuate epithelial keratopathy scores were similar in both groups. Tobramycin 0.3%/dexamethasone 0.1% significantly decreased clinical signs of ocular inflammation and total ocular inflammation scores when compared with tobramycin 0.3%/loteprednol 0.5% in patients with moderate to severe blepharokeratoconjunctivitis.

SUMMARY

A wide variety of combinations of corticosteroids and antibiotics are available in this class. Several agents are available as ointments and suspensions. There are not enough published comparative trials to distinguish any of the available products from the others.

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